UNIKLINIK KÖLN
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CLL18 / MORAI trial

an international phase-III trial aiming to establish **M**easurement **O**f **I**ndividual **R**esidual Disease for **A**djustment of treatment duration to **I**mprove outcomes in first-line treatment of CLL/SLL

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BACKGROUND:

The two major options for the first-line therapy of chronic lymphocytic leukemia (CLL) are

- a continuous BTK inhibitor treatment given as long as possible for disease control or
- a venetoclax-based fixed-duration treatment, which usually leads to deep responses and a treatment-free interval of several years.

There is an increased use of fixed-duration venetoclax-based regimens, such as venetoclax plus obinutuzumab (12 cycles) or venetoclax plus ibrutinib or acalabrutinib with/without Obinutuzumab (15 or 14 cycles). While these combination therapies are more intense compared to monotherapies, the treatment-free interval carries advantages in terms of quality of life, safety and costs.

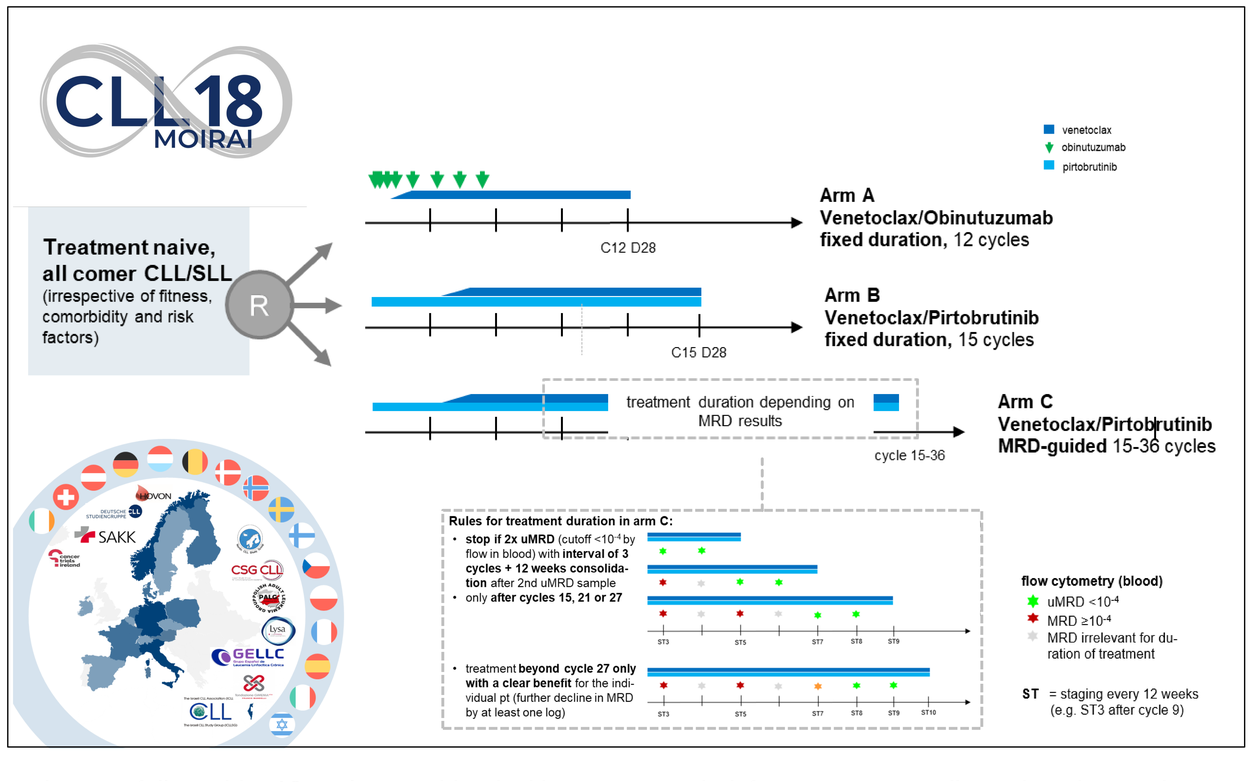
AIMS:

To evaluate if a more individualized approach is beneficial in the context of time-limited therapy, we have designed this **pan-European, academic phase III trial with three arms** - two evaluating a fixed-duration regimen and one evaluating a treatment duration based on measurable residual disease (MRD), using a treatment duration tailored to the depth of remission.

METHODS:

The standard **Arm A** is the established combination of venetoclax and obinutuzumab (Ven-Obi 12 cycles with a duration of 28 days, Obi only during cycles 1-6). **Arm B** evaluates venetoclax plus pirtobrutinib (Ven-Pirto) for 15 cycles (3 cycles pirtobrutinib monotherapy, followed by 12 cycles combined with venetoclax). In **Arm C**, Ven-Pirto will be administered for at least 15 and up to 36 cycles (as long as there is a deepening of response) until achievement of undetectable MRD (uMRD). To facilitate the transfer to clinical routine, **MRD is measured in peripheral blood by multi-colour flow cytometry and with a cut-off of 10^{-4}**. Two MRD assessments with an interval of 12 weeks both documenting uMRD are needed for a treatment discontinuation and treatment will be continued for an additional 12 weeks after the second uMRD result as a consolidation.

813 patients with previously untreated CLL/SLL irrespective of age, comorbidities or CLL risk-factors will be recruited 1:1:1 to the three arms (271 each) with a stratification according to TP53 deletion and/or mutation, IGHV mutational status, type of disease (CLL vs. SLL), and age.



The primary endpoint is the investigator-assessed progression-free survival (PFS). Secondary endpoints include iwCLL response, MRD, overall survival and safety parameters.

The CLL18/MOIRAI trial is designed to show both superiority of MRD-guided Ven-Pirto over Ven-Obi and over fixed duration Ven-Pirto.

RESULTS:

At the time of submission of this abstract, the CLL18 / MOIRAI protocol was approved by the competent authorities of 13 of the 16 participating countries. In the meantime, the trial was also approved in Italy and submitted to the authorities Switzerland, Israel is also almost ready for submission.

The first patient was recruited on June 30th at the University Hospital Cologne. As of September 10th 15 sites in Germany and one in Sweden are open and thus far, 11 pts were recruited in the trial.

The estimated recruitment time of the 813 patients in approx. 160 sites in 16 countries is 20 months.

Approximately 41 months after start of recruitment, a sufficient number of PFS events shall be reached for the primary endpoint analysis.

SUMMARY:

The CLL18/MOIRAI trial will address the question whether an individualized, MRD-guided first-line treatment with pirtobrutinib and venetoclax improves the outcome of patients with CLL/SLL compared to fixed duration venetoclax with either obinutuzumab or pirtobrutinib.

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